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(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB<sub>1</sub>-ANTAGONISTIC ACTIVITY

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring which are potent antagonists of the cannabis CB<sub>1</sub>-receptor. The compounds have the general formula (I) wherein- R and R<sub>1</sub> are the same or different and represent 3-pyridyl or 4-pyridyl or phenyl which may be substituted with halogen or methoxy-, R<sub>2</sub> and R<sub>3</sub> are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino- R<sub>4</sub> represents phenyl which may be substituted with 1 or 2 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C) and tautomers, prodrugs and salts thereof. These enantiomers are much more potent and selective antagonists of the cannabis CB<sub>1</sub>-receptor, than the other enantiomer.

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4,5-Dihydro-1H-pyrazole derivatives having CB<sub>1</sub>-antagonistic activity

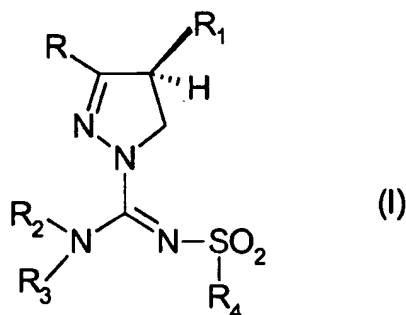
The present invention relates to a group of novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydropyrazole ring, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned (4S)-4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB<sub>1</sub>) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB<sub>1</sub> and CB<sub>2</sub>) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB<sub>1</sub> receptors in the brain, in combination with the strictly peripheral localisation of the CB<sub>2</sub> receptor, makes the CB<sub>1</sub> receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458). Hitherto, three types of distinct CB<sub>1</sub> receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB<sub>1</sub> receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* **1994**, *5*, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M.; Moerschbaeche, J.M.; Barker, L.A. *CNS Drug Rev.* **1999**, *5*, 43). Aminoalkylindoles have been disclosed as CB<sub>1</sub> receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in

1995. AM-630 is a CB<sub>1</sub> receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aryl substituted benzofurans as selective CB<sub>1</sub> receptor antagonists (e.g. LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Biorg. Med. Chem. Lett.* **1999**, *9*, 2233). Interestingly, many CB<sub>1</sub> receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334*, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1).

It has now surprisingly been found that the novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



wherein

- R and R<sub>1</sub> are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R<sub>2</sub> and R<sub>3</sub> are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R<sub>4</sub> represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen, trifluoromethyl, methoxy and alkyl (1-3 C)

are much more potent and selective antagonists of the cannabis CB<sub>1</sub>-receptor, than the correspondence R-enantiomer.

5 Due to the potent CB<sub>1</sub> antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, distonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's  
10 syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.

15 The affinity of the compounds of the invention for cannabinoid CB<sub>1</sub> receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB<sub>1</sub> receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration  
20 over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

25 The cannabinoid CB<sub>1</sub> antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB<sub>1</sub> receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB<sub>1</sub> receptors by CB<sub>1</sub> receptor agonists (e.g. CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB<sub>1</sub> receptor-mediated response can  
30 be antagonised by CB<sub>1</sub> receptor antagonists such as the compounds of the invention.

35 The invention relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

The compounds can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

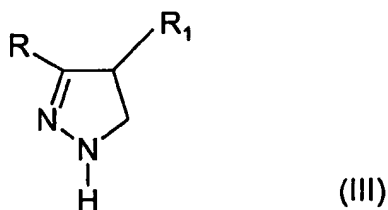
The compounds of the invention having formula (III) (*vide infra*) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689.

A suitable synthesis for the racemic compounds according to the present invention is the following:

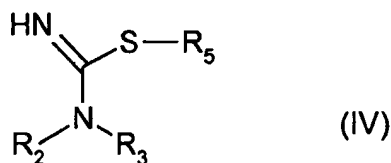
### Synthesis route A

#### Step 1 of route A

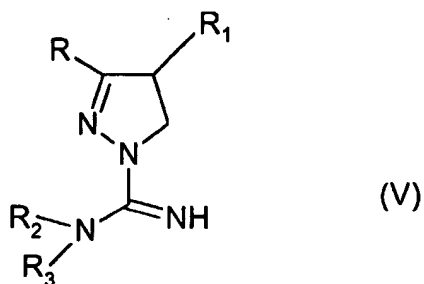
Reaction of a compound having formula (III)



with a compound having formula (IV)



wherein  $R_5$  represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)



wherein the symbols have the meanings as mentioned above. Compounds having formula (V) wherein R,  $R_1$ ,  $R_2$  and  $R_3$  have the meaning as described herein above for compound (I) are new.

Alternatively, a compound having formula (III) is reacted with a so-called guanylation agent. Examples of such guanylation agents are 1H-pyrazole-1-carboxamide and its salts (for example the hydrochloride salt) and 3,5-dimethyl-1H-pyrazole-1-carboxamide and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamide derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylation agent. Examples of such protected guanylation agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamide, N-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamide and N,N'-bis-(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamide and the like. This reaction gives after deprotection a compound having formula (V).

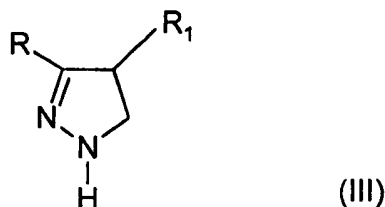
#### Step 2 of route A

The compound having formula (V) is reacted with an optionally substituted compound of the formula  $R_4\text{-SO}_2\text{X}$ , wherein  $R_4$  has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile.

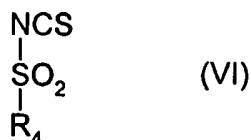
#### Synthesis route A1

##### Step 1 of route A1

Reaction of a compound having formula (III)



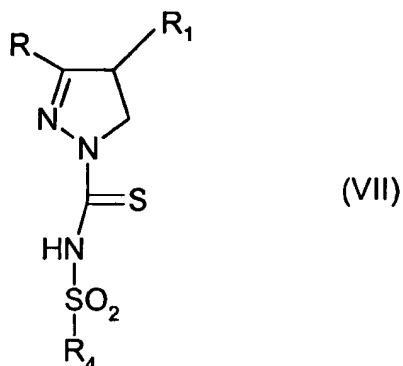
with a thioisocyanate derivative having formula (VI) .



This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

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This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R<sub>1</sub> and R<sub>4</sub> have the meaning as described herein above for compound (I) are new.



5      Step 2 of route A1

Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example HgCl<sub>2</sub>, gives a compound having formula (I)

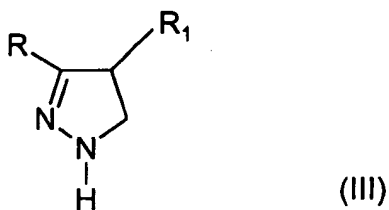
This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

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Synthesis route A2

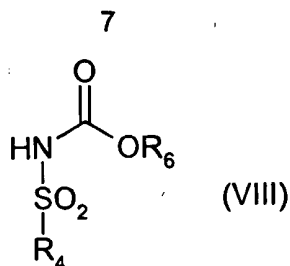
Step 1 of route A2

Reaction of a compound having formula III



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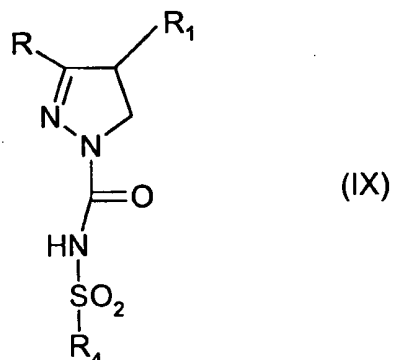
with a carbamate ester derivative having formula (VIII).



wherein  $R_6$  represents a lower alkyl group, for example methyl.

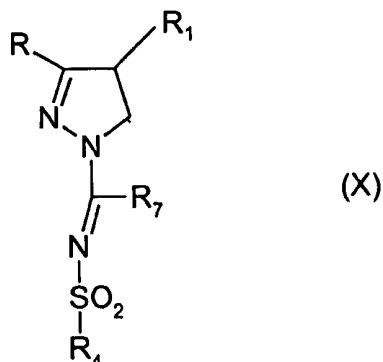
This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

- 5 This reaction gives a 4,5-dihydropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein  $R$ ,  $R_1$  and  $R_4$  have the meaning as described herein above for compound (I) are new.



Step 2 of route A2

- 10 Reaction of a compound having formula (IX) with a halogenating agent, such as for example  $PCl_5$ , gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (X).





wherein  $R_7$  represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

Compounds having formula (X) wherein  $R$ ,  $R_1$  and  $R_4$  have the meaning as described herein above for compound (I) and wherein  $R_7$  represents a halogen atom are new.

#### Step 3 of route A2

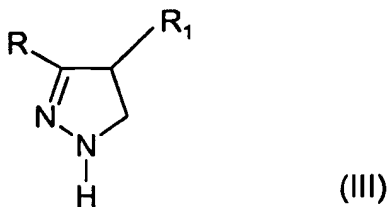
Reaction of a compound having formula (X) with an amine gives a compound having formula (I).

This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

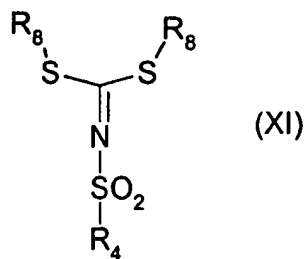
#### Synthesis route A3

#### Step 1 of route A3

Reaction of a compound having formula III

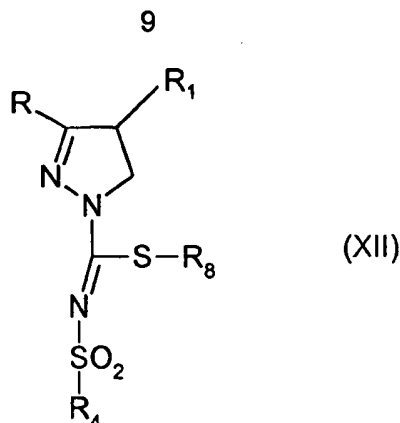


with a dithioimidocarbonic ester derivative having formula (XI) .



wherein  $R_8$  represents a  $C_{1-3}$  alkyl group.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.



This reaction gives a carboximidothioic ester derivative having formula (XII).

Compounds having formula (XII) wherein R, R<sub>1</sub> and R<sub>4</sub> have the meaning as described herein above for compound (I) and wherein R<sub>8</sub> represents a C<sub>1-3</sub> alkyl group are new.

#### Step 2 of route A3

Reaction of a compound having formula (XII) with an amine gives a compound having formula (I).

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

#### Example I

##### **3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine**

**Part A:** A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (5.1 gram, 88 % yield). Melting point: 187-189 °C.

**Part B:** To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl

chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamide (0.55 gram, 72 % yield). Melting point: 214-215 °C

In an analogous manner the compounds having formula (I) listed below have been prepared:

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamide: Melting point: 155-156 °C

4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxyphenyl)sulfonyl)-1H-pyrazole-1-carboxamide: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamide: Melting point: 221-222 °C

#### Example II

#### **N',N'-Dimethyl-N<sup>2</sup>-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide**

**Part A:** A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo*, dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

**Part B:** To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N<sup>1</sup>-dimethyl-N<sup>2</sup>-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.

#### Example III

**N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine**

**Part A:** To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-*tert*-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-*tert*-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

**Part B:** A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-

carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give

5 N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

In an analogous manner the compounds having formula (I) listed below have been prepared:

- 10 N-Methyl-N'-((3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 156-160 °C.
- N-Propyl-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 129-138 °C.
- 15 N-(2-Propyl)-N'-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 110-112 °C.
- N-(2-Propyl)-N'-((4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- N<sup>1</sup>-Ethyl-N<sup>1</sup>-methyl-N<sup>2</sup>-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 184 °C.
- 20 N<sup>1</sup>-Ethyl-N<sup>1</sup>-methyl-N<sup>2</sup>-((4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 173-176 °C.
- N<sup>1</sup>,N<sup>1</sup>-Dimethyl-N<sup>2</sup>-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-196 °C.
- N<sup>1</sup>,N<sup>1</sup>-Dimethyl-N<sup>2</sup>-((3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-198 °C.
- 25 N<sup>1</sup>,N<sup>1</sup>-Dimethyl-N<sup>2</sup>-((3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.
- N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- 30 N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 155-159 °C.
- N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- N<sup>1</sup>,N<sup>1</sup>-Dimethyl-N<sup>2</sup>-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 148-151 °C.
- 35 N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 85 °C.

Example IV**(-)-(4S)-N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide**

5 (-)-(4S)-N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (7.16 gram, 0.0147 mol) ( $[\alpha]_{\text{D}}^{25} =$   
-150°, c = 0.01, MeOH) (melting point: 169-170 °C) was obtained via chiral  
chromatographic separation of racemic N-methyl-N'-((4-chlorophenyl)sulfonyl)-3-  
10 (4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (18 gram,  
0.037 mol) using a Chiralpak AD, 20 µm chiral stationary phase. The mobile  
phase consisted of a mixture of hexane/ethanol (80/20 (v/v)) and 0.1 %  
ammonium hydroxide (25 % aqueous solution).

15 In an analogous manner the optically pure compounds listed below have been  
prepared from the corresponding racemates:

(-)-(4S)-N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-  
phenyl-1H-pyrazole-1-carboxamide: ( $[\alpha]_{\text{D}}^{25} = -126^\circ$ , c = 0.01, CHCl<sub>3</sub>); Melting  
point: 172-175 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of  
heptane/2-propanol (85/15 (v/v)).

20 (-)-(4S)-N-Dimethylamino-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-  
dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ( $[\alpha]_{\text{D}}^{25} = -132^\circ$ , c = 0.01, CHCl<sub>3</sub>);  
Melting point: 218-224 °C. Stationary phase: Chiralcel OD. Mobile phase: A  
mixture of heptane/2-propanol (85/15 (v/v)).

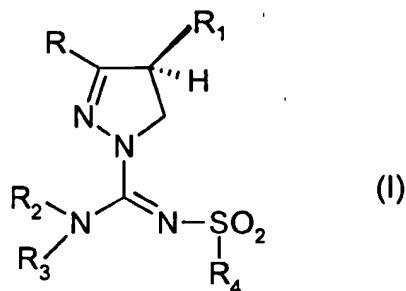
25 (-)-(4S)-N-Methyl-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-  
dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ( $[\alpha]_{\text{D}}^{25} = -131^\circ$ , c = 0.01, CHCl<sub>3</sub>);  
Melting point: 157-160 °C. Stationary phase: Chiralcel OD. Mobile phase: A  
mixture of heptane/2-propanol (85/15 (v/v)).

30 (-)-(4S)-N<sup>1</sup>,N<sup>1</sup>-Dimethyl-N<sup>2</sup>-((2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-  
dihydro-4-phenyl-1H-pyrazole-1-carboxamide: ( $[\alpha]_{\text{D}}^{25} = -88^\circ$ , c = 0.01, MeOH);  
Melting point: Amorphous. Stationary phase: Chiralpak AD. Mobile phase:  
Ethanol.

(-)-(4S)-N-Methyl-N'-((2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-  
4-phenyl-1H-pyrazole-1-carboxamide: ( $[\alpha]_{\text{D}}^{25} = -129^\circ$ , c = 0.01, MeOH); Melting  
point: Amorphous. Chiralpak AD. Mobile phase: Methanol.

**Claims**

1. The enantiomer having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of a compound of formula (I)



wherein

- R and R<sub>1</sub> are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R<sub>2</sub> and R<sub>3</sub> are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R<sub>4</sub> represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)

and tautomers, prodrugs and salts thereof.

2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R<sub>1</sub> is phenyl, R<sub>2</sub> is hydrogen, R<sub>3</sub> is methyl and R<sub>4</sub> represents 4-chlorophenyl, and salts thereof.
3. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.
4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.
5. Process for the preparation of compounds having formula I, characterized in that the racemic mixture of a compound having formula I is separated into the levorotatory and the dextrorotatory enantiomers.

- 5 6. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 10 7. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 15 8. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.



## INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 02/03079

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C07D231/06 C07D401/04 A61K31/415 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PERTWEE, R. G.: "Pharmacology of Cannabinoid Receptor Ligands" CURRENT MED. CHEM., vol. 6, 1999, pages 635-664, XP000923352 cited in the application Pages 657-659, chapter "Diarylpyrazoles"; and page 641, figure 5.	1-5
A	US 5 624 941 A (BARTH, F. ET AL.) 29 April 1997 (1997-04-29) Claim 1, formula (I); column 26, lines 27-65; column 28, lines 41-59.	1-5
A	US 4 070 365 A (VAN DAALEN, J. J. ET AL.) 24 January 1978 (1978-01-24) Claim 1; abstract.	1-5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

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- \*P\* document published prior to the international filing date but later than the priority date claimed

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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- \*Z\* document member of the same patent family

Date of the actual completion of the international search

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PCT/EP 02/03079

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 173 323 A (BAYER AG) 5 March 1986 (1986-03-05) Abstract; claim 1; page 32, example 1. -----	1-5

## INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 02/03079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5624941	A	29-04-1997	FR 2692575 A1 24-12-1993
			FR 2713224 A1 09-06-1995
			FR 2713225 A1 09-06-1995
			AT 149489 T 15-03-1997
			AU 4143893 A 06-01-1994
			BR 1100409 A3 13-10-1999
			BR 9302435 A 11-01-1994
			CA 2098944 A1 24-12-1993
			CZ 9301172 A3 16-03-1994
			DE 69308395 D1 10-04-1997
			DK 576357 T3 15-09-1997
			EP 0576357 A1 29-12-1993
			ES 2101258 T3 01-07-1997
			FI 932891 A 24-12-1993
			GR 3023535 T3 29-08-1997
			HU 64526 A2 28-01-1994
			IL 106099 A 15-07-1998
			JP 3238801 B2 17-12-2001
			JP 6073014 A 15-03-1994
			MX 9303664 A1 31-01-1994
			NO 932296 A 27-12-1993
			NZ 247961 A 28-08-1995
			RU 2119917 C1 10-10-1998
			SK 65493 A3 02-02-1994
			ZA 9304511 A 22-02-1994
			AT 154012 T 15-06-1997
			AU 685518 B2 22-01-1998
			AU 7899994 A 15-06-1995
			BR 1100984 A3 14-03-2000
			CA 2136893 A1 21-06-1995
			CN 1110968 A ,B 01-11-1995
			CZ 9403016 A3 14-06-1995
			DE 69403614 D1 10-07-1997
			DE 69403614 T2 22-01-1998
			DK 656354 T3 29-12-1997
			EP 0656354 A1 07-06-1995
			ES 2105575 T3 16-10-1997
			FI 945690 A 03-06-1995
			GR 3024470 T3 28-11-1997
			HK 1000599 A1 09-04-1998
			HU 71498 A2 28-11-1995
			IL 111719 A 28-10-1999
			JP 3137222 B2 19-02-2001
			JP 7309841 A 28-11-1995
			JP 2001026541 A 30-01-2001
			NO 944625 A 06-06-1995
			NZ 270025 A 26-09-1995
			PL 306067 A1 12-06-1995
			RU 2141479 C1 20-11-1999
			SG 68570 A1 20-06-2000
US 4070365	A	24-01-1978	NL 7409433 A 14-01-1976
			AR 223449 A1 31-08-1981
			AT 359775 B 25-11-1980
			AT 508277 A 15-04-1980
			AT 342585 B 10-04-1978
			AT 529175 A 15-08-1977
		AU	501280 B2 14-06-1979

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/03079

Patent document cited in search report		Publication date	Patent family member(s)	Publication date		
US 4070365	A		AU 8285075 A	13-01-1977		
			BE 831232 A1	12-01-1976		
			BR 7504413 A	06-07-1976		
			CA 1075242 A1	08-04-1980		
			CH 624675 A5	14-08-1981		
			CS 188962 B2	30-03-1979		
			DD 122775 A5	05-11-1976		
			DE 2529689 A1	29-01-1976		
			DK 310975 A , B,	13-01-1976		
			EG 11880 A	30-09-1978		
			ES 439292 A1	16-02-1977		
			FR 2277827 A1	06-02-1976		
			GB 1514285 A	14-06-1978		
			HU 178320 B	28-04-1982		
			IE 41836 B1	09-04-1980		
			IL 47676 A	31-01-1979		
			IT 1044358 B	20-03-1980		
			JP 1368569 C	11-03-1987		
			JP 51041358 A	07-04-1976		
			JP 61023162 B	04-06-1986		
			OA 5057 A	31-12-1980		
			PL 193676 A1	17-07-1978		
			SE 419644 B	17-08-1981		
			SE 7507868 A	13-01-1976		
			US 4156007 A	22-05-1979		
			YU 176475 A1	30-06-1982		
			ZA 7504203 A	23-02-1977		
		EP 0173323	A	05-03-1986	DE 3431926 A1	06-03-1986
					AU 4665285 A	06-03-1986
					BR 8504157 A	24-06-1986
	CA 1218366 A1			24-02-1987		
	DD 237782 A5			30-07-1986		
	DK 392985 A			01-03-1986		
	EP 0173323 A1			05-03-1986		
	ES 546559 D0			01-03-1986		
	ES 8604942 A1			01-08-1986		
	GR 852092 A1			30-12-1985		
	HU 41210 A2			28-04-1987		
	JP 61060684 A			28-03-1986		
	ZA 8506593 A			30-04-1986		